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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,697	09/17/2001	Anne-Francoise Burnol	045636-5051	8953

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,697	BURNOL ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-20* is/are pending in the application.

4a) Of the above claim(s) *14-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election **with traverse** of Group 5 (claims 8-13 as they pertain to SEQ ID NO: 5) in Paper No. 11 (20 March 2003) is acknowledged. The traversal is on the ground(s) that all the Groups as listed in the previous Office Action (Paper No. 10, 20 February 2003) share a common technical feature and no Lack of Unity issues were raised during the International Preliminary Examination. This is not found persuasive because the Groups as listed pertain to a different special technical feature, namely a unique sequence, each which is not required of the other. Concerning the second point, it is not found persuasive because the claims in the PCT application are different than the instant claims. Therefore no nexus between the claims in PCT/FR00/00613 and the instant application can be made. The Applicant final request is granted. Group 5 drawn to SEQ ID NO: 5 and Group 6 drawn to SEQ ID NO: 6 are hereby rejoined. The remaining restriction requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendments of 17 September 2001 (Paper No. 4) has been received and entered in full. Claims 1-7 have been cancelled and claims 8-20 have been added. Claims 8-13 are under examination.

3. The Applicant is *correct* as pertains the to claims listed in the Restriction Requirement mailed 20 February 2003 (Paper No. 10). The "Groups" as listed on pages 2-4 of the previous Office Action (Paper No. 10, 20 February 2003) contained typographical errors. Firstly, the Groups should have listed claims "8-13" not "1-13". Secondly, the Groups as listed should have

stated "molecules capable of modulating" and not "molecules capable of modeling". The Examiner regrets any confusion this may have incurred.

Drawings

4. The drawings are objected to because Figures 4, 5, 6, and 7 do not have labels on their respective Y-axis's. Also, the label on the X-axis's of said figures is too small to read and is off center. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

5. Claim **9** is objected to because of the following informalities: claim 9 recites non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims **10-13** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an **in vitro** method for detecting molecules capable of modulating the tyrosine kinase activity of the insulin receptor wherein the PIR domain or the PIR-SH2 domain is SEQ ID NO: 5 or SEQ ID NO: 6*, does not reasonably provide enablement for *an **in vivo** method*

for detecting molecules capable of modulating the tyrosine kinase activity of the insulin receptor using any PIR domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

7. Note that the Examiner defines "*in vitro*" (Latin for "in glass") as covering both cell based and cell-free experiments and "*in vivo*" (Latin for "in life or in living beings") to be limited to animal and patient environments (see Stedman's Medical Dictionary 27th Edition citations included).

8. The claims are directed to a method of identifying compounds which modulate the interaction of SEQ ID NO: 5 or SEQ ID NO: 6 with an insulin receptor. The claims broadly encompass all of the PIR domains or the PIR-SH2 domains of the Grb7 family of proteins. The claims also broadly encompass both *in vitro* and *in vivo* practice of the claimed method.

9. The specification teaches that an *in vitro* method for detecting molecules capable of modulating the tyrosine kinase activity of the insulin receptor using fragments of a PIR or PIR-SH2 domain as inhibitors of the insulin receptor tyrosine kinase activity.

10. A person skilled in the art would recognize that predicting the efficacy of a practicing an invention based solely on its performance *in vitro* and with only two representatives of a family of proteins is highly problematic. Thus, although the specification prophetically considers and discloses a particular mode of use of other non-SEQ ID NO: 5 or SEQ ID NO: 6 members of the Grb7 family of proteins, such a disclosure would not be considered enabling since the state of protein-protein interactions is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. The following references are cited herein to illustrate the state of the art of insulin receptors and tyrosine kinase activity.

12. Concerning the breadth of the claims, Han *et al.* (1 October 2001) "The Grb7 family proteins: structure, interactions with other signaling molecules and prudential cellular functions." Oncogene **20**(44): 6315-6321 teaches that the Grb7 family of proteins comprises Grb7, Grb10, and Grb10. However, within each member of the family, isoforms exist which vary in their binding partner specificity (pp. 6315-6316). This is further supported by Béréziat *et al.* (15 February 2002) " Inhibition of Insulin Receptor Catalytic Activity by the Molecular Adapter Grb14." The Journal of Biological Chemistry **277**(7): 4845-4852 who teaches that Grb7, Grb10, and Grb14 vary in their effectiveness in stimulating tyrosine kinase activity in insulin receptors (Figure 4). Therefore, the skilled artisan is not assured that each and every member of the Grb7 family will be able to interact and modulate the tyrosine kinase activity of the insulin receptor (IR).

13. Concerning the nature of the invention, Dong *et al.* (14 November 1997) "Cloning, Chromosome Localization, Expression, and Characterization of an Src Homology 2 and Pleckstrin Homology Domain-containing Insulin Receptor Binding Protein hGrb10γ." The Journal of Biological Chemistry **272**(46): 29104-29112 teaches an *in vitro* method of

determining the phosphorylation activity of an insulin receptor interacting with hGrb10γ using wortmannin as a control (Figure 6 and 7). In addition, Kasus-Jacobi *et al.* (13 April 2000) "Evidence for an interaction between the insulin receptor and Grb7. A role for two of its binding domains, PIR and SH2." Oncogene **19**(16): 2052-2059 teaches that the PIR domain alone, the SH2 domain alone, or the PIR-SH2 domains together absent the rest of the mature protein of Grb7 is sufficient to interact with the insulin receptor (Figure 4 and 5). However, no guidance is given in the prior art or the instant Specification as to practicing the invention *in vivo*. Therefore the skilled artisan is without guidance or examples for practicing the invention *in vivo*.

14. Due to the large quantity of experimentation necessary to identify all the applicable Grb7 family members and their respective PIR or PIR-SH2 domains, the lack of direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable PIR or PIR-SH2 domains, the absence of working examples directed to *in vivo* studies, the complex nature of the invention, the unpredictability of the effects of PIR or PIR-SH2 domains on cells and/or patients (see references above), and the breadth of the claims which fail to recite limitations for what constitutes an applicable PIR or PIR-SH2 domains, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim **10** is rejected under 35 U.S.C. 103(a) as being unpatentable over Kasus-Jacobi *et al.* (2 October 1998) "Identification of the Rat Adapter Grb14 as an Inhibitor of Insulin Actions." The Journal of Biological Chemistry **273**(40): 26026-26035 (**IDS**) in view of US 5840536 (24 November 1998) Dunnington *et al.* (**IDS**) and O'Neill *et al.* (13 September 1996) "Interaction of a GRB-IR Splice Variant (a Human GRB10 Homolog) with the Insulin and Insulin-like Growth Factor I Receptors." The Journal of Biological Chemistry **271**(37): 22506-22513 (**IDS**).

16. Kasus-Jacobi *et al.* teaches a method of bringing an activated insulin receptor into contact with Grb14's PIR domain or Grb14's PIR-SH2 domain, adding a tyrosine kinase substrate, measuring the tyrosine kinase activity (Figure 6A-B). Kasus-Jacobi *et al.* does not teach, however, adding a test molecule to be tested for its ability to modulate the tyrosine kinase activity of the insulin receptor.

17. US 5840536 teaches a method of assaying for a molecule that modulates GrbIR-1 function by bringing an activated insulin receptor into contact with GrbIR-1, adding a tyrosine kinase substrate, measuring the tyrosine kinase activity, comparing the sample with the test molecule to a sample consisting of the activated insulin receptor and GrbIR-1 (Col. 1-2). Growth factor receptor binding protein-Insulin Receptor (Grb-IR) is a cytoplasmic signaling molecule that interacts with the insulin receptor (Col. 2 lines 1-29).

18. O'Neill *et al.* teaches that Grb-IR1 is a human homolog of Grb10, a member of the Grb7 protein family thus meeting the limitations of claim 10.

19. It would have been obvious to a person of ordinary skill in the art at the time of the invention to combine the tyrosine kinase assay of Kasus-Jacobi *et al.* with the screening method of US 5840536 because US 5840536 teaches the screening method using GrbIR1, a protein related to the Grb7 family as taught by O'Neill *et al.*

20. A person of ordinary skill in the art at the time of the invention would have been motivated to combine the tyrosine kinase assay of Kasus-Jacobi *et al.* with the screening method of US 5840536 because molecules which modulate the tyrosine kinase activity of insulin receptors would be expected to be useful for the treatment of diabetes (Col. 10 lines 25-67). Further, US 5840536 teaches that the interaction of Grb-IR and the insulin receptor involves tyrosine kinase activity (Col. 2 lines 15-29) and aberrant tyrosine kinase activity is taught to be involved in diabetes (Col. 1 lines 18-35).

21. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of success because Kasus-Jacobi *et al.* and O'Neill *et al.* demonstrated a working example of the tyrosine kinase activity. Furthermore, US 5840536 provided guidance in performing an assay to screen for molecules which modulated tyrosine kinase activity.

22. Thus the invention as a whole was *prima facie* obvious over the prior art.

Summary

23. Claims 8-13 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
May 13, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER